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Anti-diabetic Drugs and Fixed Dose Combination Therapy.

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Review Article

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ABSTRACT

The Combination Therapy of different mechanism of action of drugs plays an important role in the measurement of Type II Diabetes Mellitus. The effect of diabetes develops specific complications of retinopathy, nephropathy, neuropathy, cardiac vascular diseases and cerebro vascular diseases. Combination therapy is beneficial for various diseases over monotherapy. The oral hypoglycemic drug combination therapy is most suitable for chronic disorder. Sulfonyl ureas, Alpha glucosidase inhibitors, Biguanides, Meglitinides and Thiazolidinediones are important in Combination Therapy. Bilayer tablet is suitable for sequential release of two drugs in combination, in which one layer is initial dose as immediate release and second layer is maintenance dose. This article explains the dual therapy of bilayer tablet and combination of anti-diabetic drugs which improves the patient compliance and provides synergistic effect.

INTRODUCTION

Diabetes is a group of metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. [1] Diabetes mellitus mainly classified into two categories, Insulin dependent diabetes mellitus when the pancreas does not produce enough insulin to properly control blood sugar levels, in this condition the patient completelydepends parental formulation of insulin another one Non-insulin dependent diabetes mellitus, the cells of the body become resistant to insulin which are treated with oral antidiabetic agents such as Sulfonylureas, Biguanides, Thiazolidinediones derivatives, carbohydrate analogue and DPP- 4 inhibitors.

Facts of diabetes

The development of diabetes projected to reach pandemic proportion over the next 10-20 years. Diabetes mellitus may present with characteristic symptoms such as thirst, polyuria, blurring of vision, and weight loss.Often Symptoms are not severe, or may be absent, and consequently hyperglycaemia sufficeint to cause pathological and functional changes may be present for a long time before the diagnosis is made. In the presence of marked hyperglycaemia in newly diagnosed symptomatic Type II diabetes (HbA1c > 8%, FPG>11.1 mmol/L, or RPG > 14mmol/L), an oral anti-diabetic agents can be considered at the outset together with lifestyle modification. Globally, the number of diabetes patients has risen sharply. While in 1985, 30 million people had diabetes, the number rose to 150 million in 2000. In 2010, 285 million people (6.6% of the global population in the age group 20-79) were found to be diabetic. However, by 2030, an estimated 435 million people are expected to suffer from this disease 7.8% of the adult population. The burden of diabetes is enormous and escalating at an alarming rate. Nearly 26 million Americans have the disease, including over 10% of the total adult population and over 25% of the population aged 65 years and older. While most of those individuals have Type II diabetes, nearly 1million Americans have Type I diabetes. An additional 79 million American adults have prediabetes, when added to those with diabetes, suggests that nearly half of the adult population currently has impaired glucose

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metabolism. Diabetes will cost the world economy near $376 billion in 2010 or 11.6% of total world healthcare expenditure. Though India will spend only 1% of the total diabetes spending worldwide, the amount itself is staggering $2.8 billion. US, on the other hand, will account for $198 billion or 52.7% of the total diabetes spending worldwide. By 2030, diabetes is expected to cost the world economy $490 billion. [2]

Bilayer tablets [3,4,5]

The bilayer tablet is usually introduced to improve patient compliance, eliminate frequent dosing and fluctuation in plasma drug concentrations. The dual therapy mainly used to achieve the rapid and extended release of drugs from the formulation. The rapid or immediate release layer containing the loading dose provides a rapid rise of drug concentration. The second layer provides the maintenance dose and prevents the fluctuations of therapeutic concentration of the drug in the body. Various approaches for bilayer tablets. [6]

- Multilayered Tablets – two or three component system
- Compression Coated Tablets – tablet within a tablet coated partially surrounding the core
- Inlay Tablets

Advantages of Bilayer Tablet

- Improve the patient compliance
- Economic
- Synergistic Effect
- Maintain Physical & Chemical Stability
- Retain potency and ensure dose accuracy

Disadvantages of Bilayer Tablet

- Labour cost is high
- Layer separation
- Cross contamination between the layers

Types of Bilayer Tablet Press

- Single sided tablet press
- Double sided tablet press
- Bilayer tablet with displacement monitoring

Management of Diabetes Mellitus and Fixed dose Combination (FDC) therapy

Depending upon the condition of the patient, some factors to be taken into account for the treatment

- Degree of hyperglycemia
- Properties of Antihyperglycemic drugs
- Co-Morbidity condition.
  Management of Diabetes Mellitus can be classified into mainly two
  a) Oral medicines b) Combination medicine [6,7]
- Oral Monotherapy drugs and the Mechanism of Action (MOA) was discussed in the Table No. 1

Oral monotherapy drugs and the mechanism of action (MOA)

Table 1

Drug Class	Drug Name	Brand Name	Mechanism of Action
Biguanides	Metformin	Glucophage	Inhibit glucose production by the liver
Sulfonylureas (second-generation)	Glimepiride Glipizide Glyburide	Amaryl Glucotrol Diabeta Glynase PresTab Micronase	Increase Insulin secretion by pancreatic beta cells
Meglitinides	Repaglinide Nateglinide	Prandin Starlix	Increase Insulin secretion by pancreatic beta cells
Thiazolidinediones (TZDs)	Pioglitazone Rosiglitazone	Actos Avandia	Increase glucose uptake by skeletal muscle
Alpha-glucosidase inhibitors	Acarbose Miglitaol	Precose Glyset	Inhibit carbohydrate absorption in the small intestine

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Need for combination therapy [7, 8]

Fixed dose combination therapy (FDC) is called as a combination of two or more actives in a fixed ratio of doses. The International Diabetic Federation (IDA) and American Diabetic Federation (FDA) tend to suggest if the monotherapy fails along with lifestyle modification the patient should followed by combination therapy. Combination therapy based on the rationale of a multi targeted approach and it helps to achieve and maintain the desired therapeutic targets. The advantages of Fixed Dose Combination are easy of administration, convenience, synergistic effect, complementary mechanism of action, with low dose less side effects, economical, reduce the pill burdenand thereby, improve adherence to treatment, improve tight glycemic control, decrease the incidence/severity of Adverse Drug Reactions, delay the need for insulin therapy.

Previously various works have been done with the combination of diabetes drugs in bilayer tablets which are shown in the Table No. 2 [3,4,5] and Table No.3.

Currently Fixed Dose Combination (FDC) of diabetic drugs are fabricated for various reasons which are discussed in the Table No.4.

Table 2: Combination of Diabetes Drugs in Bilayer Tablets

Drug (s)	Reason
Glibenclamide +Metformin HCL	Reduce the frequency of administration, Improve the patient compliance
Pioglitazone+ Metformin HCL	Improve the patient compliance
Metformin HCL +Gliclazide	Prolong the release upto 12hrs and improve the patient compliance
Glimepiride + Metformin HCL	Improve oral therapeutic efficacy with optimal control of plasma drug level
Pioglitazone + Gliclazide	Provide synergistic action
Glipizide +Metformin HCL	Provide synergistic action

Table 3 : Marketed available Combination medicines for Diabetes mellitus [6]

Drug (S)	Brand name
Voglibose + Metformin	Voliix
Metformin+Glipizide	Metaglip
Saxagliptin+MetforminER	Kombiglyze XR
Sitagliptin +Metformin	Janumet R
Vidagliptin +Metformin	GalvumetR
Metformin+Rosiglitazone	Avandamet R
Glimepiride+ Metformin	Diapred-m2
Metformin + Glimepiride	Glycifit G1, Glycifit G2
Metformin (SR) + Glimepiride and Pioglitazone	Glycifit Trio G1
Metformin + Glimepiride +and Pioglitazone	Glycifit Trio G2
Metformin + Voglibose	Glycifit V 0.2, Glycifit V 0.3
Sitagliptin,+Metformin	Istamet
Gliclazide+ Metformin	Diamicron XR
Pioglitazone+ Metformin	Pioglu
Glimepiride+ Metformin	Gluconorm

Table 4 : List of Current Fixed Dose Combinations(FDCS) [9]

Combination of Drugs	MOA	Rationale
Metformin+ Sulfonyl Urea	Metformin suppresses hepatic gluconeogenesis to reduce fasting glycemia and the peripheral glucose uptake sulfonyl ureas increase insulin release from β cells residual function is present	Better than monotherapy, Provide synergistic effect of Type II diabetes
Metformin+ Pioglitazone	Pioglitazone increases insulin sensitivity in lives and adipose tissue and inhibit β cell loss	Synergistic effect of Type II diabetes
Metformin+ DPP(IV) inhibitors	Inhibits the breakdown of GLP-1 by DPP-4 therefore increases GLP-1 levels, resulting in increased glucose-dependent insulin release and decreased level of circulating glucagon and hepatic glucose production	Safety and tolerability (mainly used for early combination therapy)
Metformin+ Alpha Glucosidase Inhibitors	Metformin acts on gluconeogenesis to target glycemic and Acarbose, voglibose reduce intestinal glucose absorption to control post pradiel glycemia	Provide synergistic effect of Type II Diabetes

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CONCLUSION

Fixed Dose Combination therapy of oral hypoglycemic drugs is more suitable for Type II Diabetes mellitus. Bilayer tablets are single pharmaceutical dosage form provides synergistic action, therapeutic justification and reduce the capital investment. Bilayer tablet is quality and GMP requirements can vary widely.

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